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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,218	HORIUCHI, YOSHIHIRO	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-11,15-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 18* is/are rejected.

7)☒ Claim(s) *1-6,8-11,16,17 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Final Rejection

The Status of Claims

Claims 1-6, 8-11,15-18, and 20 are pending.

Claims 15 and 18 are rejected.

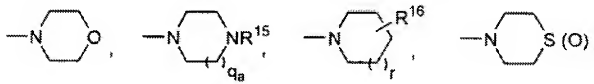
Claims 1-6, 8-11,16-17, and 20 are objected.

Claim Objections

The objection of Claims 1, 7,10 has been withdrawn due to the modification and cancellation of the claims ,whereas regarding the claim 6, the objection of Claim has been maintained due to the failure to modify the claim.

Furthermore, in view of the revised claims, there are some issues to be resolved.

In claim 1, chemical terms" heteroaryl group, heteroaryloxy group, heteroaryl thio group, heteroarylsulfonyl group, heteroarylcarbonyl group" and "



"

are recited.

All those limitations are directed to the non-elected group II; they must be removed from the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Applicants' argument filed 4/11/08 have been fully considered but are not persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 1-12 and their corresponding dependent claims under 35 U.S.C. 112, first paragraph, has been withdrawn due to the cancellation and modification of claims.

However, due to the revised claims, there are some issues to be resolved.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a disease related to MMP-3 and /or MMP-13 for arthritis, does not reasonably provide enablement for all kinds of diseases related to MMP-3 and /or MMP-13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to include those diseases unrelated to the invention commensurate in scope with these claims.

The claim is directed to not the specific diseases, but all kinds of the diseases by using the mechanistic nature of inhibiting matrix metalloproteinase enzymes such as MMP-3 and /or MMP-13. The specification falls short because data essential for treating many diseases by means of inhibiting matrix metalloproteinase enzymes is not described in the specification.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claim 15 is the method for treating a disease related to promotion of MMP-3 and/or MMP-13 comprising administering a hydroxamic acid compound or pharmaceutically acceptable salt thereof, according claim 11, as an active ingredient top a patient in need thereof.

The State of the Prior Art

The state of the prior art is that according to US Patent No. 5,948,780, MMP inhibitors have been used to prevent and treat congestive heart failure and other cardiovascular diseases. Recent data has revealed that specific enzymes are closely related to some diseases ,while there is no effect on other diseases. The MMPs are generally classified based on their substrate specificity; particularly , the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave interstitial collagen tissue. This has been noticed by the discovery that only MMP-13 is over expressed in breast carcinoma, whereas MMP-1 alone is over expressed in papillary carcinoma (see Chen

et al., J. Am .Chem. Soc., 2000;122;9648-9654). Furthermore, according to Wo/01/63244A1 and US Patent No. 6,008,243 few selective inhibitors of MMP-13 have been approved: however, no selective or nonselective inhibitor of MMP-13 has been approved for treating any disease in any animal.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that inhibitng the enhanced level of MMPs would result in only the specific site of the interstitial collagen tissue; this kind of treatment can not translated to all the possible treatment of any disease in regards to their therapeutic effects.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compounds of formula I and the promotion of matrix metalloproteinase, one of skill in the art is unable to fully predict possible results from the administration of the claimed compounds of formula I due to the unpredictability of the role of inhibiting the enhanced level of MMPs in any patient for treating purpose, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of ex. 2 can inhibit the MMPs which helps in the treatment for adjuvant arthritis. However, the specification is silent and fails to provide guidance as to whether the diseases listed (pages 46-48) require the inhibition of the MMPs for treatment, i.e. the specification fails to provide a correlation between the diseases listed and the inhibition of the MMPs. Also, there is no direction and guidance for the inhibition of the MMPs for the treatment of any kinds of diseases.

The presence or absence of working examples

There is no working example except for the treatment of arthritis using the ex. 2 compound. Furthermore, there are not other working examples for any other diseases listed in the specification. Also, the compounds which are discloses in the specification have no pharmacological data regarding the treatment of any other disease besides inhibitory activity of various MMPs using compounds from various classes and have no data on the possible treatment of the various diseases that require the inhibitory activity of various MMPs. Also, the specification fails to provide working examples as to how

the listed diseases can be treated by the inhibition of various MMPs, i.e. again, there is no correlation between the diseases listed and inhibition of various MMPs.

The breadth of the claims

The breadth of the claims is that the compounds of formula I can treat any disease by the inhibition of the MMPs , without regards as to the affect of the inhibition of the MMPs on the stated diseases.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the inhibition of the MMPs and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of the MMPs.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I for the treatment of any disease by the inhibition of the MMPs. As a result, necessitating one of skill to perform an exhaustive search for which

diseases can be treated by the compounds of formula I in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Enablement for the scope of "inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and

biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear

sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 1-18 under 35 U.S.C. 112, second paragraph, has been withdrawn due to the cancellation and modification of claims.

however, due to the revised claims, there are some issues to be resolved.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 15, the phrase" a method for treating a disease related to promotion of MMP-3 and/or MMP-13" is recited. This expression is vague and indefinite because the promotion of MMP-3 and/or MMP-13 can be led to treat any kinds of diseases; there is uncertainty as to how closely the promotion of MMP-3 and/or MMP-13 is related to treating any disease. Appropriate correction is required.

Applicants' Argument

Applicants argue the following issues:

a.

> Regarding claim 6, the phrase "2-pyridyl group, 3-pyridyl group, 4-pyridyl group, furyl group, thienyl group (the said pyridyl group, furyl group and thienyl group may be substituted by lower alkyl group)" means the group represented by R^3 alone. Contrary to the assertion of the Examiner, this group does not belong to Group II, and thus is not directed to non-elected subject matter.

Applicants' arguments have been noted, but the arguments are not persuasive.

First, regarding the applicants' argument , the Examiner has noted applicants' arguments. However, as indicated in the above, all those heteroaryl or heterocyclic limitations are directed to the non-elected group II; they must be removed from the claims. Therefore, applicants' argument is not persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taylor Victor Oh/
Primary Examiner, Art Unit 1625

7/18/08